REMARKS

Claims 1-13 are pending in the application. The Examiner has previously rejected these claims, finalizing the rejection in an Office Action dated April 2, 2002. Applicant later filed a Notice of Appeal along with additional arguments traversing each of the asserted grounds for rejection. In an Advisory Action dated July 22, 2002, the Examiner rejected these arguments and maintained the rejection. During a phone interview with the Examiner and her supervisor, Long Le, on October 23, 2002, Applicant was invited to submit its further arguments traversing the rejection. In a subsequent Non-final Office Action dated December 30, 2002, and in view of Applicant's phone discussion and arguments, the Examiner withdrew all grounds for rejection of the claims and asserted new rejections. Applicants now respond to each rejection in turn.

Rejection Of Claims 1-3 and 5-9 Under §103(a)

Claims 1-3 and 5-9 were rejected under 35 U.S.C. §103(a) as being unpatentable over Kim *et al*, U.S. Patent No. 5,648,225 ("Kim") in view of Loken et al, U.S. Patent No. 5,047,321 ("Loken"). For the reasons presented below, however, reconsideration and withdrawal of the rejection respectfully is solicited.

Kim discloses a multipurpose reagent for rapid analysis of a whole blood sample. (Abstract). In one embodiment disclosed by Kim, "a nuclear stain, e.g., ethidium homodimer, is added to the multipurpose reagent system before it is added to [a] blood sample." (Column 8, lines 35-38). Another embodiment discloses "mixing flourochrome-conjugated monoclonal antibodies... with whole blood samples before adding the multipurpose reagent system." (Column 9, lines 1-5).

Loken discloses a method for multi-parameter analysis of cells in a body fluid sample comprising two nucleic acid dyes and at least one fluorescently labeled cell surface marker (abstract). Loken further discloses analyzing said sample in an automated instrument capable of detecting and recording fluorescence of individual cells (col. 4, lines 37-40).

Loken further states:

> *"In contrast with peripheral blood, two populations of bone marrow cells were identified having low orthogonal light scatter signals and dimly expressing (CD45 antigen, colored purple and light blue respectively in Figure 4b. From this figure it is obvious that there is not clear separation between the populations of cells colored light blue and the other painted populations. Light microscopic examination of the population of cells which expressed the lowest level of CD45 antigen (purple), revealed that it consisted exclusively of normoblasts and erythroblasts (Table I). The population expressing slightly higher amounts of CD45 antigen (light blue) contained the most immature cells including monomyeloid and lymphoid precursors and a few erythroblasts (Table I)."*

Loken, Column 10, lines 23-37.

The Examiner acknowledges, however, that Kim fails to disclose simultaneously analyzing samples to discriminate erythroblasts by detecting nucleotide fluorescent signals and to determine leucocyte classes by detecting signals from labeled antibodies bound to cell surfaces antigens on leucocytes. (Paper 30, page 4).

To fill the acknowledged gap, the Examiner cites Loken for disclosing combining a whole blood sample with at least two nucleotide fluorescent dyes and at least one fluorescent labeled antibody; the dyes assessing "different characteristics of nucleated cells in the sample and simultaneously, the fluorescent labeled antibody..." assessing leucocytic cells. (Paper 30, pages 4-5).

The Examiner then states it would have been obvious to one having ordinary skill in the art to simultaneously analyze blood samples to discriminate erythroblasts by detecting

nucleotide fluorescent signals and to determine leucocyte classes by detecting signals from labeled antibodies bound to cell surface antigens on leucocytes because Loken teaches "multiparametric flow cytometer analysis [which] "*allows*" for such simultaneous measurements," (emphasis added) and that the multipurpose reagent system of Kim is "*capable*" of performing both functions simultaneously. (Office Action, p. 5).

Where the citations are silent, they cannot be said to "allow" or be "capable" of anything. The terminology used is inapt and only serves to thinly veil the Examiners' speculative arguments. And the rejection is plainly founded upon mere speculation that the references can be combined. As Applicants have stated so many times previously "the mere fact the references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." MPEP §2143.01 (2000 Ed., 2100-98) Citing, *In re Mills*, 16 USPQ2d 1430 (Fed. Cir. 1990) (emphasis original). "Allowing" for a certain result and being "capable" of performing a function are mere opinions and not evidence that the citations suggest, motivate or disclose the desirability of the proposed combination. In essence, the rejection improperly rests on the Examiners articulating a possibility that the cited references can be combined, not that there is any actual or identifiable suggestion, motivation or disclosure to do so.

In contrast to the Examiners' rationale, sufficient motivation to combine the cited references to adequately support the rejection requires the Examiner to demonstrate the kind of motivation which would have "*strongly motivated*" one to make a process as claimed, *Ex parte Graselli*, 231 USPQ 393, 394 (Bd. Appeals. 1983). The type of motivation required is that which would have "*impelled*" one to do so, *In re Levengood*, 28 USPQ2d at 1302, and the type

of suggestion required is one that demonstrates the selection and combination "*should*" be made, *Ex parte Markowitz*, 143 USPQ 303, 305 (Bd. Appeals. 1964).

In comparison to these requirements, the motivation invoked to support the combination underlying the rejection is clearly insufficient. The references should not be considered in light of the objectives achieved by the Applicants' invention. *In re Ochiai*, 37 USPQ2d 1127, 1133 (Fed. Cir. 1995) ("reliance on *per se* rules of obviousness is legally incorrect and must cease."); and see MPEP §2116.01 at 2100-45 (Seventh Edition, Rev. 1, Feb. 2000). Unfounded manipulations of the reagent system disclosed in Kim, using the disclosure of Loken, absent any consideration of the compatibility of the respective systems, does not provide the factual grounds necessary for supporting the rejection. *Ex Parte Porter*, 25 USPQ2d 1141, 1147 (BPAI 1992). Nor does the interpretative exercise of determining what the citations "allow" or are "capable" of.

Absent any motivation to combine, the Examiners strain to provide their own hindsight motivation to support the rejection. This endeavor takes place entirely outside the actual disclosures of Kim and Loken and is improper. For instance, Applicants pointed out previously to the Examiner that Kim discloses two separate embodiments, one where a stain is mixed, and one where monoclonal antibodies are added first to a blood sample. Applicants argued that the claims were not anticipated because Kim did not disclose adding or using ***both*** a monoclonal antibody and a nuclear stain in the same process. The Examiners agreed and withdrew the rejection.

Nonetheless, in raising the instant rejection based on obviousness, the Examiners allege that Kim's deficiency as an anticipating reference (i.e., the "gap" in the disclosure of Kim that is filled by combining Loken) is Kim's failure to disclose using its multipurpose reagent to

simultaneously discriminate erythroblasts and determine leucocyte classes. The Examiners then proceed to explain that because Loken arguably achieves both objectives, Loken provides the motivation to modify the disclosure of Kim and so render the claims obvious. To this inventive misapplication of Kim and Loken, Applicants, however, respond, "Not so fast!"

What Loken discloses is not so pliable. Loken discloses: use of two nucleotide dyes and one fluorescent labeled antibody; measuring the intensity of three types of fluorescence and one type of scattered light; producing two scattergrams; and performing one gating. In this manner a group that includes erythroblasts, among other components, is identified. Loken does not disclose discrimination and counting of erythroblasts within this group. In fact, as illustrated in the above quotation from Loken at Column 10, lines 23-37, Loken fails to even teach discrimination of erythroblasts from other cells in the group.

Therefore, combining Loken does not motivate modification of Kim's processes or its reagent to discriminate erythroblasts based on the intensity of fluorescence from a nuclear stain and a labeled antibody. Even if the intensity of fluorescence from the cell-surface marker of Loken is combined with the intensity of fluorescence from a nuclear stain to produce a scattergram, Loken fails to disclose discrimination of erythroblasts, as is apparent from Figure 1C and column 8, lines 34-36 of Loken. Both Kim and Loken define: the respective stains they use; the respective parameters they measure; and the respective order of measurement in analyzing a blood sample. Taking these respective elements, *ad hoc*, out of their contexts in Kim or Loken finds neither motivation within these citations, nor any support more than the Examiners' opinion illustrating that this is "allowed" or "capable." Nothing demonstrates this selective isolation and combination of Applicants' claimed elements would achieve the results

claimed, absent undue experimentation and/or deliberation. The rejection is demonstrably improper and should be withdrawn. Applicants respectfully request such action.

Rejection of Claims 4 and 10-13 Under §103(a)

Claims 4 and 10-13 were rejected under 35 U.S.C. §103(a) as being unpatentable over Kim and Loken, and further in view of U.S. Patent No. 5,298,426 issued to Inami, *et al.* ("Inami"). Applicant traverse this finding. Reconsideration and withdrawal of the rejection respectfully is solicited.

Kim and Loken have been previously described.

Inami discloses a method comprising mixing blood with a first fluid comprising a dye and a pH buffer and mixing this solution with a second fluid comprising a buffer to neutralize acidity in the first solution. (Inami, column 2, lines 3-10). The sample is then analyzed in a flow cytometer and a two-dimensional plot of fluorescence and scattered light is made. (Column 2, lines 15-21).

In making the instant rejection, the Examiner relied on Kim and Loken, as discussed previously. The Examiners acknowledged, however, that neither Kim nor Loken disclose permeabilizing cell membranes by incorporating reagents and buffers at specific pH and osmolarity parameters in a two step method. (Paper 30, page 6)

To fill the acknowledged gap, the Examiner relied on Inami for "disclosing" "mixing blood with a hypotonic fluorescent dye solution capable of diffusing into erythroblasts to stain their nuclei and a buffer for maintaining pH in the acidic range." (Paper 30, page 6). The Examiners further relied on Inami for "disclosing" mixing the (acidic) sample mixture with

a second fluid comprising a buffer that neutralizes the acidic pH in the solution to a value at which the shape and integrity of the leukocytes are maintained." (Paper 30, page. 6).

The Examiners then contended that it would have been obvious to combine the teachings of Kim, Loken and Inami because, according to the Examiners:

> *"Kim specifically taught that integrity and antigenicity of white blood cells need to be maintained optimally during permeabilization, i.e. lysing, of the nRBC's or erythroblasts so as to allow accurate simultaneous quantitation of both populations, as suggested by Loken, sometimes requiring quenching of lytic activity of the reagent because of its damaging effect to leukocytic populations and Inami specifically taught that such a procedure eliminates such extreme lysing conditions for erythroblasts while maintaining the integrity and shape of WBCs for accurate differentiation of both erythroblast and leukocyte populations"* (Paper 30, page 8).

The Examiners further acknowledge, as to Claims 11-13, that neither Kim, Loken or Inami disclose differentiating between different stages of erythroblast populations. The Examiners address this deficiency by stating that "Inami can effectively perform the same erythroblast maturity differentiation and quantitation as set forth in instant Claims 11-13 upon subjecting the sample mixture to flow cytometry." (Paper 30, page 8).

The deficiencies in the Examiners' §103 rejection are plain. For reasons already discussed, Kim and Loken are insufficient to support rejection of Claim 1, from which claims 4, and 10-13 ultimately depend. Moreover, the addition of Inami to the unmotivated combination of Kim and Loken adds only further weight to a structurally flawed foundation. Kim and Loken demonstrably cannot support the further combination of Inami. For this reason alone the rejection is improper and should be withdrawn.

Notwithstanding the deficiencies of Kim and Loken, neither motivates modifying their respective processes to include the method disclosed in Inamai. Moreover, Inami does not

disclose use of antibodies. Inami therefore does not disclose the limitation of Claim 4 of admixing a first reagent fluid after the step in Claim 1, (i), of staining with a fluorescent labeled antibody. Rather, Inami discloses mixing blood first with a first solution that contains a nucleotide dye and a buffer. Therefore, Inami, even combined with Kim and Loken as the Examiners suggest, fails to account for the elements and limitations of the claims at issue.

It is fundamental to a rejection under §103 obviousness that the cited references account for *all* claimed elements and limitations. *In re Royka*, 180 USPQ 580 (CCPA 1974). Furthermore, it is also fundamental that, to reject claims to a method, the references relied upon by the Examiner must account for the manipulative steps claimed. *In re Magat*, 112 USPQ 317, 319 (CCPA 1957). It is simply not sufficient to account only for material and structural limitations without accounting for the affirmative active steps in the order directed by the claim that act upon, in, or with them. The rejection therefore fails.

Moreover, as the Examiners admit, Kim, Loken, and Inami all fail to account for other manipulative steps in Applicant's claims in not disclosing differentiating between different stages of erythroblast populations. The elements of Claims 11-13 are therefore unaccounted for in the citations and the rejection must fail. Accounting for the deficiency and what the Examiners deem Inami, despite its silence, "can effectively perform", does not substitute for actual disclosure in the citations. Moreover, no claim of inherency or other evidence supports the Examiners' contention that somehow Inami teaches, without disclosing, performance of the same steps.

CONCLUSION

In sum, the Examiners have not adduced factual support demonstrating the requisite motivation for the combination of references advanced against Applicants' claims. In addition, as combined, the citations fail to account for all the Applicants' claim limitations and lack disclosure teaching or suggesting their combination. The Examiners have not met their burden of demonstrating a *prima facie* case of obviousness, therefore, the rejection should be withdrawn.

In view of the foregoing, favorable action on the merits, and allowance of all claims, respectfully is solicited.

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to the Commissioner for Patents, Washington, D.C. 20231, on April 30, 2003.
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